Combining risks:

Implications for uncertainty analysis

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*The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

Topics to be covered

- Review of some relevant topics
  - Dose addition and response addition
  - Dose-response models vs. safety assessments
- Adding cancer risks
  - Current practice
  - Implications of adding cancer risks
- Combining effects other than cancer
  - Current practice and some issues
- Some future applications of dose addition
  - Example: TCE

Response addition

- Assumes that the stressors behave ***independently*** of one another in terms of toxicokinetic and toxicodynamic processes.

$$p(d_1, d_2, \ldots) = 1 - \Pi (1 - p_i)$$

$$= \Sigma\, p_i + [\text{cross-product terms}]$$

$$\approx \Sigma\, p_i$$

where d_i is the dose of stressor i

p_i is the probability of a response following exposure to a dose d_i of stressor i

Dose addition

- Assumes that the stressors behave ***similarly*** in terms of toxicokinetic and toxicodynamic processes.

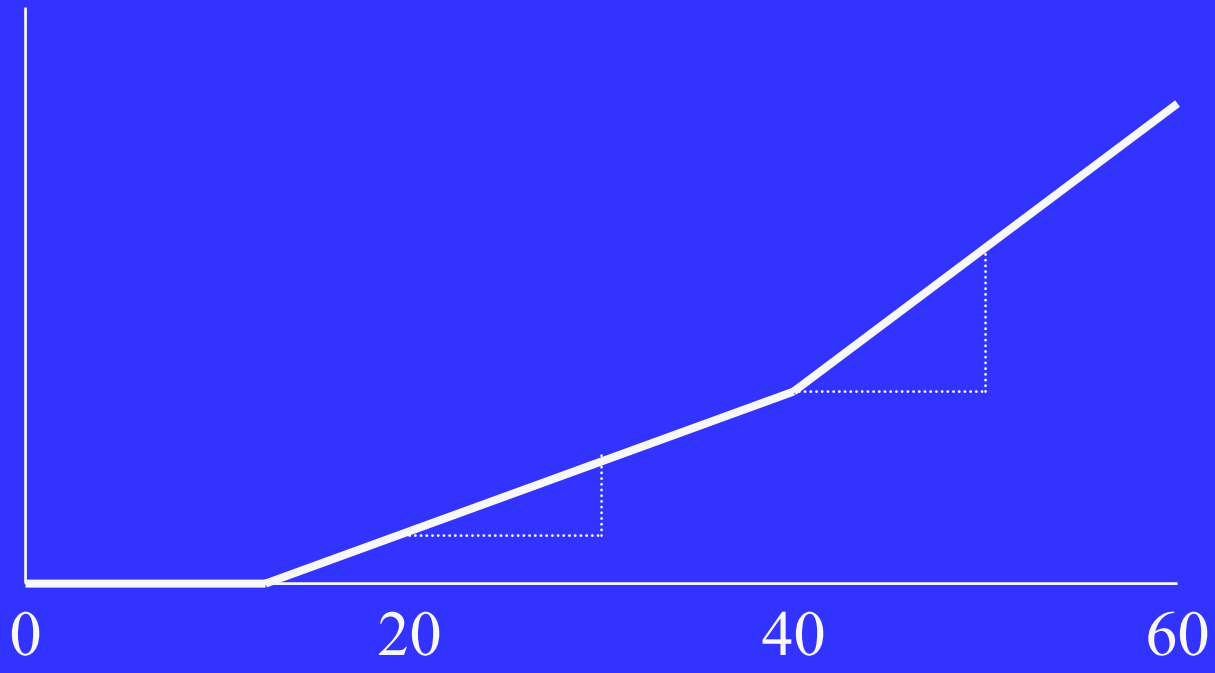
- Assumes a constant proportionality between effective doses of the stressors.

$$p\,(d_1,\ d_2,\ \ldots) = f\,(\Sigma\ r_i\,d_i)$$

where d_i is the dose of stressor i
r_i is the relative potency of stressor i

- Some examples:
  - TEFs for dioxins, furans, coplanar PCBs
  - Relative potency factors for some carcinogenic PAHs.

Dose addition is really important with nonlinear dose-response curves



The response depends on the overall level of exposure.

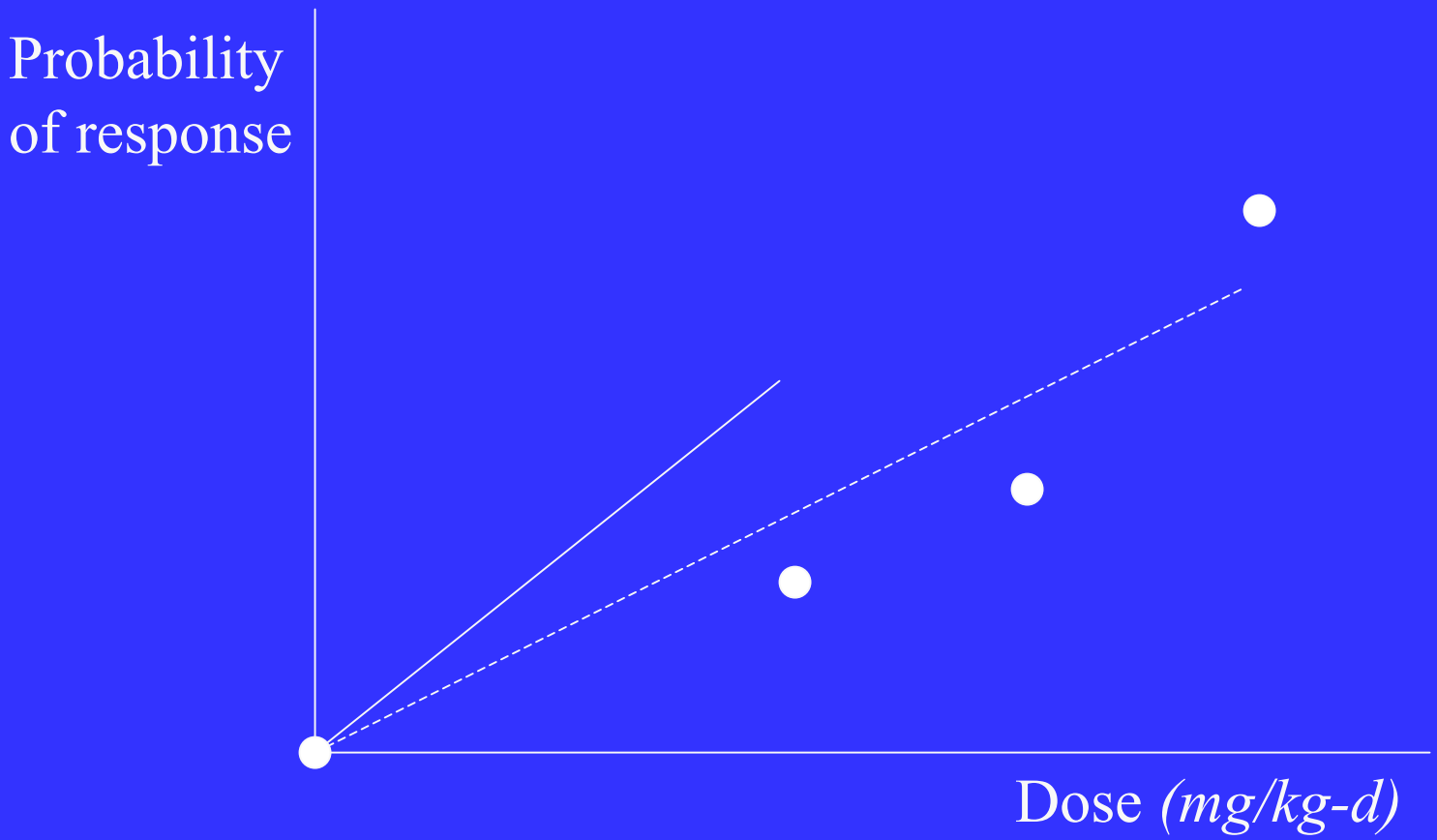
A dose that appears safe in the absence of other exposures may not be safe when background exposures are considered.

Two types of dose-response estimates

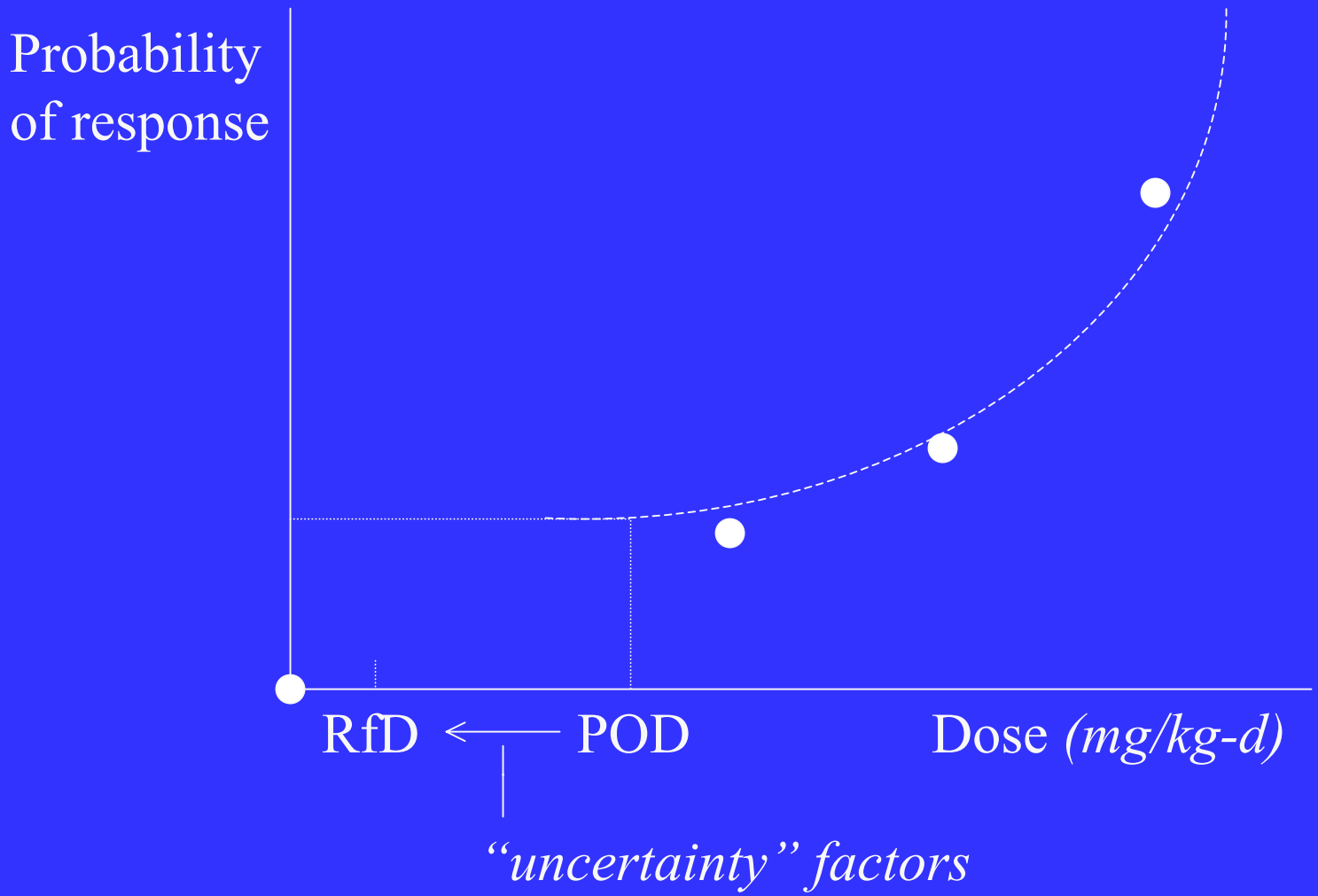
- Dose-response model that characterizes risk as a probability over a range of environmental exposure levels.

- Safety assessment that characterizes the safety of one lower dose, with no explicit characterization of risks above or below that dose.

Example of a dose-response model



Example of a safety assessment



Current practice for adding cancer risks

- When risks are estimated, response addition is typically used.

$$\text{risk}\,(d_1, d_2, \ldots) \approx \Sigma\, p_i$$

$$= \Sigma\,(\text{SF}_i \times d_i)$$

- Because slope factors are plausible upper bounds, this is often criticized as “adding conservative estimates to conservative estimates.”

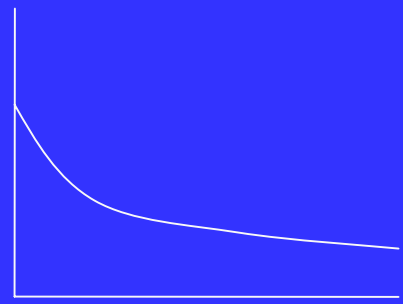
Two ways to view adding plausible upper bounds

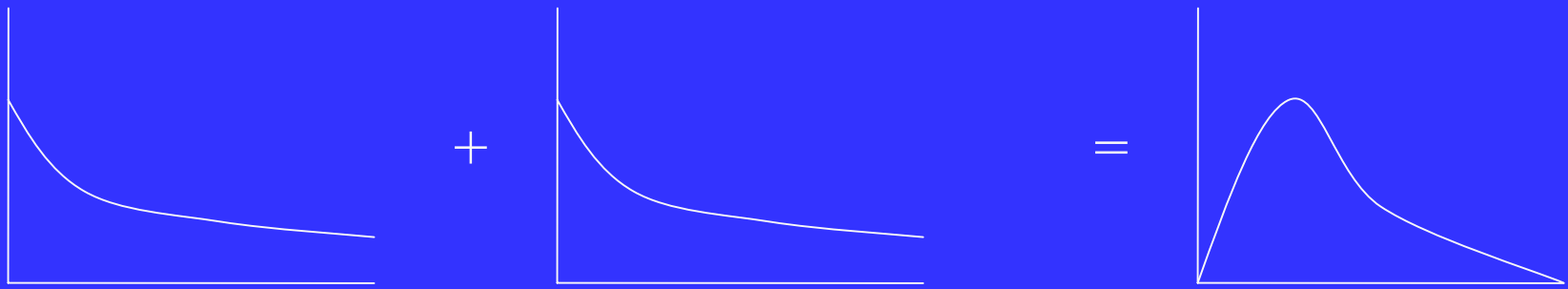
- Does the sum of upper bounds yield an ***improbable*** estimate of the overall risk?

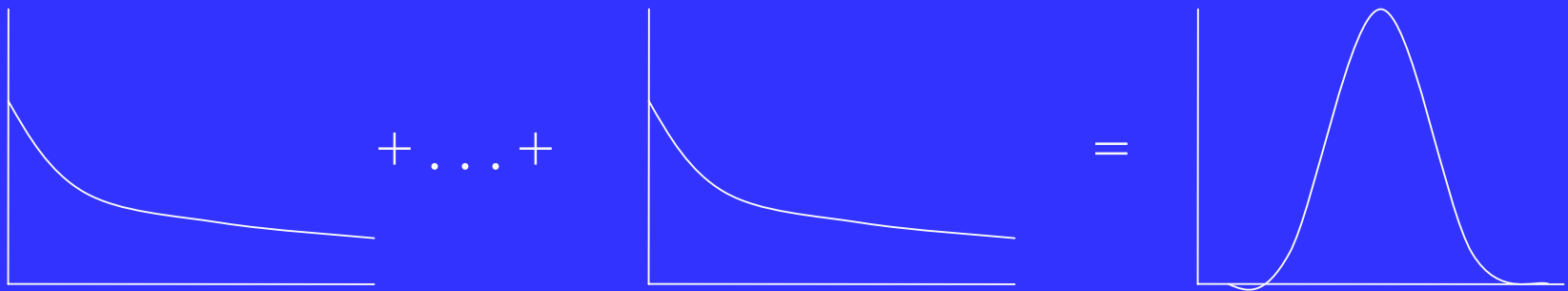
- Does the sum of upper bounds yield a ***misleading*** estimate of the overall risk?

What happens when we add plausible upper bounds?

One risk, distributed between 0 and its upper bound:







Conclusions about adding plausible upper bounds

- As more risks are added, the sum becomes increasingly ***improbable*** as an estimate of the overall risk.
- **BUT** the sum is ***not misleading*** as an estimate of the overall risk.
- **MOREOVER**, the sum can be ***adjusted*** to yield a more plausible upper and lower bound on the overall risk.

Source: Cogliano (1997) Risk Analysis 17(1): 77-84.

Adjusting a sum of plausible upper bounds to bound the overall risk

No. of risks	Symmetric distribution	Exponential distribution	Severe skew	Risks of different sizes
5	Σ/2.8 - Σ/1.4	Σ/6.1 - Σ/1.3	Σ/32.3 - Σ/1.7	Σ/3.0 - Σ/1.3
10	Σ/2.4 - Σ/1.5	Σ/5.5 - Σ/1.9	Σ/9.7 - Σ/2.2	Σ/2.7 - Σ/1.4
20	Σ/2.2 - Σ/1.6	Σ/4.6 - Σ/2.2	Σ/6.8 - Σ/2.5	Σ/2.6 - Σ/1.5

Sources of conservatism in a cumulative risk assessment

- An individual slope factor may not be plausible.
- Multiplying an upper-bound slope factor by an upper-bound exposure estimate does compound conservatism.

BUT ONLY TO A MINOR EXTENT:

- Adding plausible upper bounds together.

Current practice for combining effects other than cancer

- Risks are generally not estimated for effects other than cancer, a safety assessment (RfD or RfC) is used instead.

- These RfDs and RfCs are generally combined using a ***hazard index***, which is based on dose addition:

$$HI = \Sigma \, (d_i \, / \, RfD_i)$$

- Depending on the nature of the assessment, this sum can be taken over different groups of chemicals:
  - Screening assessments: all chemicals with RfDs.
  - Superfund assessments: common target organ.
  - FQPA assessments: common mode of action.

Some harmonization issues

- How to add oral and inhalation doses when the target organ is not the site of contact.
- How to include effects that are not the critical effect for a particular chemical.

Some future applications of dose addition

- Common mode of action
- Common metabolites

TCE: an example of multiple sources of exposure to its toxic metabolites

- Among TCE's toxic metabolites are TCA and DCA.

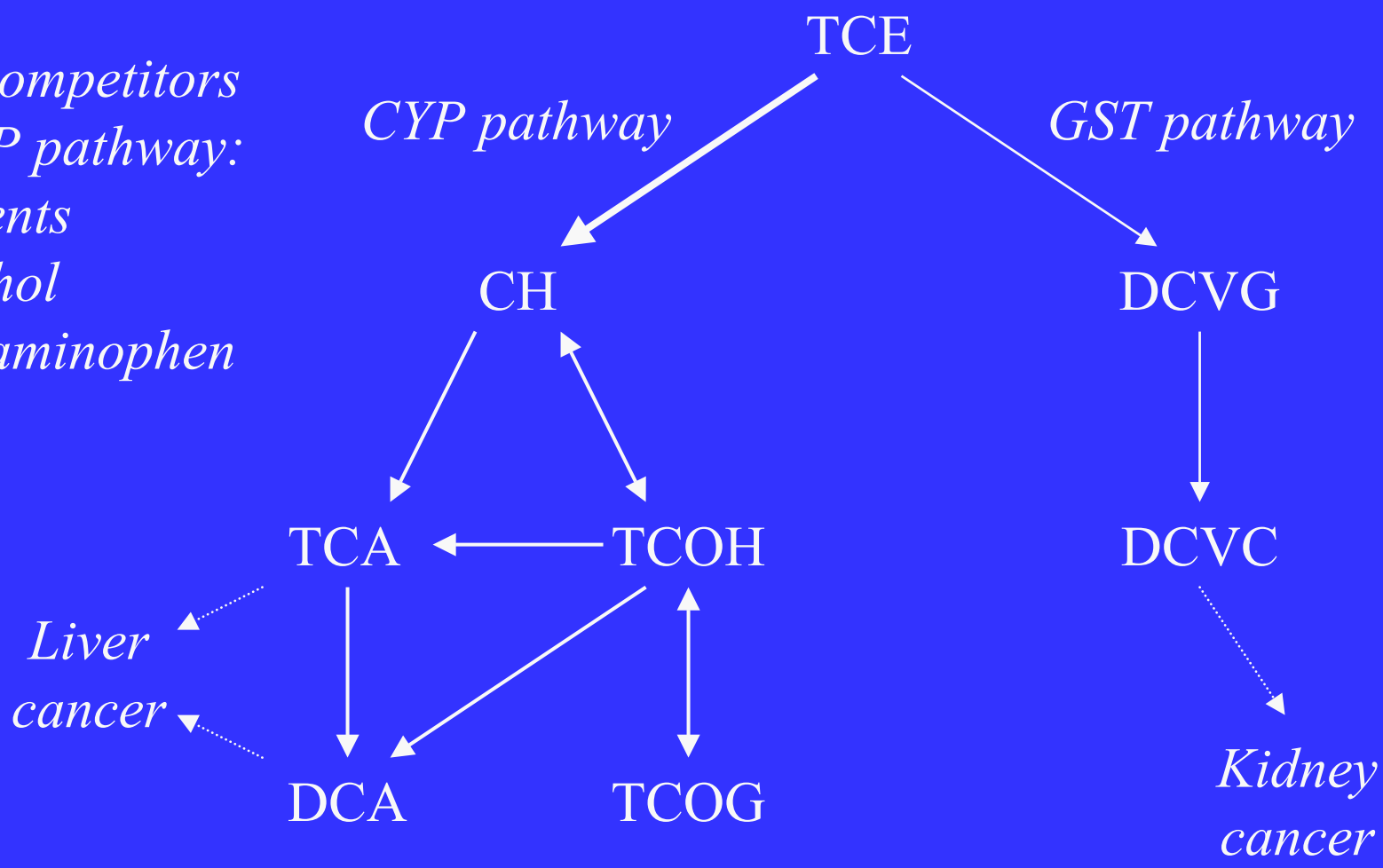
- A direct source of exposure to TCA and DCA:
  - These are byproducts of drinking water chlorination.

- Indirect sources of exposure to TCA or DCA:
  - These are metabolites of some chlorinated solvents.

- The risk from TCE depends on:
  - Level of exposure to TCE.
  - Sources of direct exposure to TCE's metabolites.
  - Other compounds that produce these metabolites.
  - And more . . .

TCE: an example where cumulative exposures can alter metabolism

Some competitors for CYP pathway:
- *Solvents*
- *Alcohol*
- *Acetaminophen*



TCE: SAB advice on metabolic interactions

- Commended EPA for addressing this question.
- An adjustment factor can be used to account for the difference in internal levels of TCE's toxic metabolites in the presence or absence of concurrent exposures to other agents that alter TCE's metabolism.
  - Adjustment factor can kept separate for application when interactions are expected.
  - Adjustment factor can be part of the toxicity values if interactions generally would be expected.
  - Up to EPA to decide how to implement this, consistent with its cumulative risk framework.